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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,541	02/27/2002	Tatsuya Haga	31671-176438	1435
26694	7590	10/13/2004	EXAMINER	
VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP			NICHOLS, CHRISTOPHER J	
P.O. BOX 34385			ART UNIT	
WASHINGTON, DC 20043-9998			PAPER NUMBER	
			1647	

DATE MAILED: 10/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/069,541

Applicant(s)

HAGA ET AL.

Examiner

Christopher J Nichols, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-7, 11-13, 15-18, 22-25, 27-33, 35, 36, 38-63, 66 and 68-112 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☒ Claim(s) 100, 102, 105, 110, and 111 is/are allowed.
- 6) ☒ Claim(s) 99, 101, 103, 104, 106-109 and 112 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) See Continuation Sheet are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 February 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2.27.02.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-7,11-13,15-18,22-25,27-33,35,36,38-63,66 and 68-98.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 2-7,11-13,15-18,22-25,27 33,35,36,38-63,66 and 68-112.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 September 2004 has been entered.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed on 27 February 2002 has been received and entered in full.
3. The Amendment filed on 21 September 2004 has been received and entered in full.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

5. All Objections to the claims as set forth at ¶4-6 pp. 2 in the previous Office Action (26 May 2004) are *withdrawn* in view of Applicant's amendments (21 September 2004).
6. The Rejection of claims **100, 102, and 105** as set forth at ¶7-20 pp. 3-8 in the previous Office Action (26 May 2004) are *withdrawn* in view of Applicant's amendments (21 September 2004).
7. The Rejection of claims **110-112** under 35 U.S.C. §112 ¶1 as set forth at ¶21-33 pp. 9-16 in the previous Office Action (26 May 2004) are *withdrawn* in view of Applicant's amendments (21 September 2004).
8. The Rejection of claim **102** under 35 U.S.C. §112 ¶1 as set forth at ¶34-45 pp. 16-19 in the previous Office Action (26 May 2004) are *withdrawn* in view of Applicant's amendments (21 September 2004).
9. The Rejection of claims **99, 104, and 108** under 35 U.S.C. §112 ¶2 as set forth at ¶50-54 pp. 21 in the previous Office Action (26 May 2004) are *withdrawn* in view of Applicant's amendments (21 September 2004).
10. The Rejection of claims **110-111** under 35 U.S.C. §112 ¶1 as set forth at ¶55-57 pp. 21-22 in the previous Office Action (26 May 2004) are *withdrawn* in view of Applicant's amendments (21 September 2004).

New Objections And/Or Rejections

Specification

11. The disclosure is objected to because of the following informalities: missing space “μMhemicholinium” (pp. 14). Appropriate correction is required.

Allowable Subject Matter

12. Claims **100, 102, 105, 110, 111** are free of the art.

Claim Rejections

Claim Rejections - 35 USC § 101

13. Claims **108, 109, and 112** are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 108 and 109 recite “host cell” while claim 112 recites “A cell”, all are products of nature and as such are non-statutory subject matter. The Examiner respectfully suggests amending the claims to read “An isolated host cell” and “An isolated cell” to obviate this rejection.

Claim Rejections - 35 USC § 112

14. Claims **99, 101, 103, 104, 106, 107, 108, and 109** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated gene comprising an amino acid sequence represented by SEQ ID NO: 6, an isolated polypeptide encoded by SEQ ID NO: 5, isolated host cells and fusion proteins comprising same, does not reasonably provide enablement for a protein comprising an amino acid sequence where one or a few amino acids are deficient, substituted, or added in the amino acid sequence represented by SEQ ID NO: 6 or isolated protein encoded by the nucleic acid of SEQ ID NO: 5 wherein one or a few amino acids*

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are deficient, substituted, or added, variants, fragments, and/or derivatives thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the reasons as set forth at ¶4-6 §2 in the previous Office Action (26 May 2004).

15. Applicant traversed the rejection of the previously presented claims in the Response filed (21 September 2004). The relevant grounds of Applicant's arguments are responded to herein:

(a) it is a matter of routine experimentation for a skilled artisan to make and test variants where one or a few amino acids are deficient, substituted, or added into the amino acid sequence.

16. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

17. On "(a)", Applicant's arguments and claim construction constitute an invitation to experiment. No specific guidance is present in the Specification or the prior art as to what constitutes an acceptable mutation or variation of the claimed sequence or the claimed proteins.

18. Claims 99, 101, 103, 104, and 106-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons as set forth at ¶34-45 §16-19 in the previous Office Action (26 May 2004).

19. Applicant traversed the rejection of the previously presented claims in the Response filed (21 September 2004). Applicant's arguments have been taken into consideration and are not found persuasive because Applicant has failed to evidence material possession of the invention

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as claimed. MPEP §2145 clearly states that attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection (MPEP § 2129 and §2144.03).

20. Furthermore, the arguments of counsel cannot take the place of evidence in the record. In the instant case the Applicant is asserting that the Specification teaches variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 or encoded by the nucleic acid of SEQ ID NO: 5 that retains the desired high-affinity choline transporter activity while no data, information, or teaching supports variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 or encoded by the nucleic acid of SEQ ID NO: 5 that retains the desired high-affinity choline transporter activity in the instant Specification {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) (“An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.”) and MPEP § 716.01(c)}.

21. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 6 or encoded by the nucleic acid of SEQ ID NO: 5, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

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22. Claim **103** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "stringency" in claim 103 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention for the reasons as set forth at ¶¶46-49 §19-21 in the previous Office Action (26 May 2004).

23. Applicant traversed the rejection of the previously presented claims in the Response filed (21 September 2004) that "stringent conditions" are known in the art.

24. To satisfy the requirements of 35 U.S.C. §112 ¶2 Applicant must unambiguously define the limitations of the claims. "Stringent conditions" for hybridization, while known the art, are not unambiguously defined. A great deal of latitude and a range of conditions may be construed as "stringent". Also, stringency may be low, moderate, or high, none of which is specified by the claims as instantly neither presented nor supported by the Specification. For instance, the Roche website defines hybridization conditions under four parameters: temperature, pH, concentration of monovalent cations, and the presence of organic solvents, none of which are defined by the claims or the Specification ("Nucleic Acid Hybridization- General Aspects" pp. 33-37 Roche website retrieved on 12 May 2004). Also the NIH Division of Intramural Research teaches that "Nucleic Acid Hybridization" conditions vary. For temperature it teaches that it may be 25°C below duplex melting temperature, which varies due to the length of the polynucleotide and the GC content. Also, salt concentrations may vary between 5 to 6x SCC and denaturing agents such

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a formamide ranges from 1% to 50% (NIH Division of Intramural Research "Nucleic Acid Hybridization" retrieved from NIH website on 12 May 2004).

25. Furthermore Umansky *et al.* US 6,287,820 states:

Numerous equivalent conditions can be employed to comprise either low or high stringency conditions; factors such as the length and nature (DNA, RNA, base composition) of the probe and nature of the target (DNA, RNA, base composition, present in solution or immobilized, etc.) and the concentration of the salts and other components (e.g., the presence or absence of formamide, dextran sulfate, polyethylene glycol) are considered and the hybridization solution can be varied to generate conditions of either low or high stringency hybridization different from, but equivalent to, the above listed conditions. The term "hybridization" as used herein includes "any process by which a strand of nucleic acid joins with a complementary strand through base pairing" (Coombs, Dictionary of Biotechnology, Stockton Press, New York N.Y. [1994].

"Stringency " typically occurs in a range from about $T_m - 5^\circ\text{C}$. (5°C below the T_m of the probe) to about 20°C . to 25°C . below T_m . As will be understood by those of skill in the art, a stringent hybridization can be used to identify or detect identical polynucleotide sequences or to identify or detect similar or related polynucleotide sequences.

26. Therefore, stringent hybridization can be used to detect similar or related polynucleotide sequences, but there is no definite limit as to how similar or related the polynucleotide sequences have to be, and the claims are indefinite.

27. Therefore the skilled artisan is not apprised of the metes and bounds of what constitutes "stringent conditions". Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined. Incorporation of those conditions which Applicant feels defines the term "stringent conditions" into the claims would obviate the rejection. For instance pp. 37 of the instant Specification lists hybridization conditions as "50% formamido, 5X SSPE, 5X Denhardt's Solution, 0.5% SDS, 100 $\mu\text{g/ml}$ salmon sperm DNA at 42°C .

Claim Rejections - 35 USC § 102

28. Claims **99, 104, and 108** are rejected under 35 U.S.C. 102(b) as being anticipated by Busch *et al.* (August 1998) “Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine.” Mol Pharmacol. **54(2)**: 342-52.

29. Busch *et al.* teaches the isolation, cloning, expression, and functional characterization of hOCT2, cation transporter from human brain (pp. 333-343; Figure 5). Busch *et al.* teaches hOCT2 is expressed in the hippocampus, specifically pyramidal cells (Figures 2-3). The Examiner notes that Kandel *et al.* Principles of Neural Science (Box 45-1 pp. 890-895) teaches that the hippocampus is rich in cholinergic cells thus meeting the limitations of claims 99 and 104. Busch *et al.* teaches that the hOCT2 is expressed as a recombinant protein in Oocytes and shows uptake of choline thus meeting the limitations of claim 108 (Figures 8-9).

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN

October 8, 2004

Elizabeth C. Hummer

ELIZABETH C. HUMMER
PRINCIPAL EXAMINER